

Application No.: 10/521,958  
Filing Date: January 21, 2005

## REMARKS

### Interview, Petition for Suspension of Action and Response filed September 8, 2008

Applicants thank Examiner Jean-Louis and her Supervisor, Sreeni Padmanabhan, for the courtesy of a personal interview on June 30, 2008 which is summarized herein. This interview summary is identical to the summary provided with the September 8, 2008 response.

With the September 8<sup>th</sup> response, Applicants presented a petition for suspension of action under 37 C.F.R. § 1.103(a) to provide time to obtain data for additional surfactants similar to the data submitted in the first Declaration under 37 C.F.R. § 1.132 of Makoto Kanebako and Hitomi Chiba provided with the January 16, 2008 response. The petition was granted in a letter dated November 14, 2008. Applicants now have additional data which is submitted herewith in the form of a second Declaration under 37 C.F.R. § 1.132 of Makoto Kanebako and Hitomi Chiba.

### The gel-cream formulation of the invention

A gel-cream formulation includes both 20-50 wt% of alcohol and 7-30 wt% of oil as components. The gel-cream formulation of the claimed invention has good solubility of indomethacin and exhibits an excellent absorbability of the indomethacin through the skin due to the high (20-50 wt%) alcohol composition. Furthermore, the gel-cream formulation of the invention does not stick to the skin after it is used due to the oil component (7-30 wt% oil).

That is, the gel-cream formulation of the invention has the advantage of both a conventional gel formulation and a conventional cream formulation. Due to the high oil content, the gel-cream formulation of the claimed invention avoids the disadvantage of the conventional gel formulation which gives a “poor use” feeling and also avoids the disadvantage of the conventional cream formulation which has poor absorbability of indomethacin through the skin.

While gel-cream formulations are known, what has not been known and which is the problem solved by the invention is prevention of separation of the gel-cream formulation into oil and water layers due to the large amount of alcohol present in the gel-cream formulation. This problem is solved by the presently claimed invention and the resulting commercial products are marketed in Japan.

Applicants present the following comparison between the claimed invention and the cited prior art documents. The Examiner is referred to Exhibit A, attached hereto, which is identical to the color version which was discussed and presented at the interview.

**Rejection under 35 U.S.C. § 103(a)**

Claims 1 and 3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kimura, et al. (JP 10-182458) (Kimura).

The formulation described in Example 2 of Kimura, et al. is a cream formulation. This formulation comprises a total amount of 25 wt% of medium chain fatty acid triglyceride and diisopropyl adipate as oil component but no alcohol so phase separation is not a problem.

The formulation disclosed in Example 3 of Kimura, et al. is a gel formulation. This formulation comprises 30 wt% of modified ethanol as an alcohol, but comprises only 3 wt% of an oil component (diisopropyl adipate). Because the oil component is low and outside the range of Applicants' claimed invention (see Table in upper left side of Exhibit A), phase separation is not a problem.

Indeed, Kimura avoids combining high oil and high alcohol in the same formulation, presumably to completely avoid the phase separation problem that is addressed by Applicants' claimed invention.

Although the Examiner agrees that Kimura, et al. do not teach all of the elements of the claimed invention, present claims 1 and 3 are rejected as obvious, particularly in light of paragraph 0008 of Kimura, et al. which teaches "a surface active agent (a sorbitan fatty acid ester and a glycerine fatty acid ester, Polyglyceryl fatty acid ester, propylene glycol fatty acid ester, Polyoxyethylene sorbitan fatty acid ester, polyoxyethylene sorbitol fatty acid ester, Polyoxyethylene glycerine fatty acid ester, polyethylene glycol fatty acid ester,...)".

However, Kimura, et al. only teach surfactants which are generic to the specific surfactants claimed by Applicants. Kimura, et al. do not teach that the surfactant must have a melting point of 40 °C or higher. While the Examiner argues that such characteristic would be inherent (Office Action, page 3, paragraph 1), such property would not be inherent to the disclosure of Kimura, et al. because not all of the surfactants taught by Kimura, et al. have a melting temperature of 40 °C or higher. Only specific species within the various genera

described by Kimura would fall within the scope of the claims. Furthermore, there is no guidance in Kimura, et al. for one of ordinary skill in the art to address the technical problem of phase separation defined and solved by Applicants. The disclosure of paragraph 0008 of Kimura, et al. is merely a generic disclosure that does not specify either the size of the polymer or the nature of the fatty acid.

The Examiner argues that Kimura teaches the exact same surfactant as in the presently claimed invention (polyethylene glycol monostearate). Presumably, the Examiner refers here to Example 3. Example 2 also teaches surfactants which are within the scope of Applicants' claims. However, as discussed above, Example 2 describes an external cream agent and does not have an alcohol component. One of ordinary skill in the art would not add an alcohol component to the formulation of Example 2 because one of ordinary skill in the art would have expected the combination of oil and alcohol to result in phase separation. Accordingly, even though Example 2 teaches both the surfactant and oil components along the lines claimed by Applicants, Example 2 does not teach all of the claim elements and it would not be reasonable for one of ordinary skill in the art to modify Example 2 to add other components (thereby coming to the same invention as claimed by Applicants) because one of ordinary skill in the art would want to avoid phase separation.

Likewise in Example 3, while alcohol in the range of Applicants' claimed invention and polyethylene glycol monostearate are taught, one of ordinary skill in the art would not have further combined an oil component as one of ordinary skill in the art would have wanted to avoid phase separation.

The Examiner rebuts Applicants' arguments that the gel of Kimura is unpleasant and sticky because the gel formulation (Example 3, discussed above) has the same surfactant (polyethylene glycol monostearate) and would therefore inherently have the same characteristics. However, in reality, the gel of Example 3 would not be expected to have the same characteristics of the claimed gel-cream formulation because the property of "good feel" is not due to the surfactant but to the presence of the oil component which is lacking in the formulation of Example 3 of Kimura. As discussed above, the role of the surfactant in Applicants' preparations is to prevent phase separation of the oil and aqueous (alcohol) phase. As the formulations of Kimura are different from Applicants' claimed formulation, they also lack the advantageous

properties of Applicants' claimed invention of "good feel" in combination with high absorption of indomethacin.

The Examiner also appears to identify the "good feel" and high indomethacin absorption properties of the claimed composition as an intended use. However, these properties of the claimed composition are a direct result of the inventive combination of 25-50 wt% alcohol, 7-30 wt% of oil component combined with a surfactant "selected from the group consisting of glyceryl monostearate, sorbitan monostearate, stearyl alcohol, and polyethylene glycol monostearate, wherein the component selected from the group consisting of glyceryl monostearate, sorbitan monostearate, stearyl alcohol, and polyethylene glycol monostearate has a melting point of 40°C or higher" and flow directly from this combination. Accordingly, properties of "good feel" and superior absorption of indomethacin should be taken into account in determining patentability.

The Examiner also mentions that Kimura teaches 20% of adipic acid oil in example 2 (Office Action, page 7, paragraph 1). However, Kimura teaches "diisopropyl adipate" not "adipic acid oil". Furthermore, the concentration is 5%, not 20%. As discussed at the interview of June 30<sup>th</sup>, the concentrations of Kimura's components are given after the naming of the ingredient, not before. Applicants respectfully submit that these comments are in error.

The following remarks are supplemental to the Response filed on September 8, 2008.

As discussed at the Interview of June 30, 2008, the Declaration under 37 C.F.R. § 1.132 of Makoto Kanebako and Hitomi Chiba submitted with the response of January 16, 2008 (1<sup>st</sup> Declaration), presented results for polyethylene glycol monostearate, one of the surfactants recited in claim 1, that were unexpected.

In Table 2 of the 1<sup>st</sup> Declaration, 40EO (Polyethylene glycol monostearate; formulation 10) having a melting point of 42-47°C was compared to 4EO (Polyethylene glycol monostearate; formulation 15) having a melting point of 31-36°C (also see Table 3). As shown in Table 2, when polyethylene glycol monostearate, m.p. 31-36°C, is included as surfactant in a gel-cream formulation with high oil (7% as per the claimed invention), there is phase separation after one month. When polyethylene glycol monostearate, m.p. 42-47°C, is included in the formulation, there is no phase separation, even at two months. This result shows the criticality of the high melting point, at least for polyethylene glycol monostearate, and was unexpected.

Application No.: 10/521,958  
Filing Date: January 21, 2005

With this submission, Applicants present the 2<sup>nd</sup> Declaration of Makoto Kanebako and Hitomi Chiba (2<sup>nd</sup> Declaration) which shows similar data for the additional three claimed surfactants: glyceryl monostearate, sorbitan monostearate and stearyl alcohol. As with the data above for polyethylene glycol monostearate in the 1<sup>st</sup> Declaration, each of the 3 surfactants is compared to multiple analogs having a lower (less than 40°C) melting point. In each case, there was no phase separation in the gel-cream formulations having a melting point of 40°C or higher, but phase separation was always observed when the melting point of the surfactant analog was below 40°C.

Applicants respectfully submit that the combined 1<sup>st</sup> and 2<sup>nd</sup> Declarations support the criticality of the melting point of 40°C or higher as claimed for all of the claimed components and that the showing is commensurate with claim scope. Applicants respectfully submit that the indomethacin external gel-cream having "one or more components selected from the group consisting of glyceryl monostearate, sorbitan monostearate, stearyl alcohol, and polyethylene glycol monostearate...[and having] a melting point of 40°C or higher" as claimed is patentable over the cited references.

In view of the above Remarks taken with the Remarks submitted with the Response of 9/8/08 and the 1<sup>st</sup> and 2<sup>nd</sup> Declarations under 37 C.F.R. § 1.132, Applicants respectfully request reconsideration and withdrawal of the rejections.

In view of Applicants' arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

#### Rejection under 35 U.S.C. § 103(a)

Claims 1 and 3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Inagi, et al. (US 4309414) (Inagi).

Example 4 of Inagi, et al. is a gel formulation, similar to Example 3 of Kimura, et al. (discussed above). The gel formulation of Inagi, et al. comprises 30 wt% of ethanol as an alcohol, but comprises only 2 wt% of oil component (diisopropyl adipate) so that the phase separation problem does not occur here.<sup>1</sup>

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<sup>1</sup> Note that the polyethylene glycol 300 of Inagi, et al. is different chemically from polyethylene glycol monostearate as recited in claim 1 of the present invention. The chemical formulas are

**Application No.: 10/521,958**  
**Filing Date: January 21, 2005**

Inagi does not teach either a cream or a gel-cream formulation.

The Office Action refers to col. 2, lines 14-16 as teaching addition of an oil component (Office Action, page 6, lines 2-3; 2<sup>nd</sup> full paragraph). However, the components listed here are more properly classified as surfactants, rather than oils.

The Office Action also states that polyethylene glycol 300 is the same as polyethylene glycol 300 monostearate which is incorrect. At the interview of June 30<sup>th</sup>, technical bulletins for these compounds were submitted so that they could be clearly distinguished (see interview summary herein; Examiner's interview summary under "Exhibit shown or demonstration conducted" (indicated as "samples of the prior art references"); and Exhibit B and C attached hereto).

Accordingly, Inagi does not teach all of the elements of the claimed invention. In view of Applicants' arguments, withdrawal of the rejection is respectfully requested.

#### **No Disclaimers or Disavowals**

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

#### **CONCLUSION**

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different as illustrated by the technical bulletins provided at the interview (Handbook of Pharmaceutical Excipients, 3<sup>rd</sup> edition, Arthur H. Kibbe, ed.) and provided herewith as Exhibits B and C.

Application No.: 10/521,958  
Filing Date: January 21, 2005

In view of the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Dec 3, 2008

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